
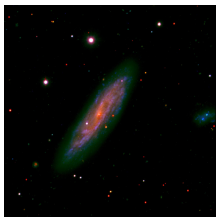
LBT & Image

"X-RAY RESONANT IRRADIATION AND HIGH-Z RADIOSENSITIZATION IN CANCER THERAPY USING PLATINUM NANO-REAGENTS"

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Astronomy

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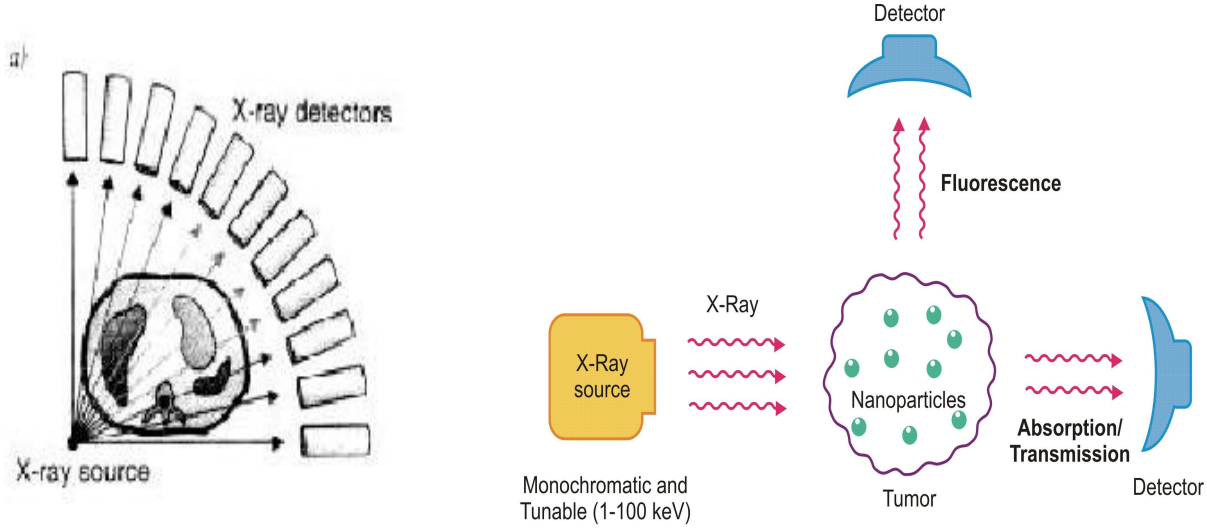
RNPT METHOD FOR CANCER TREATMENT

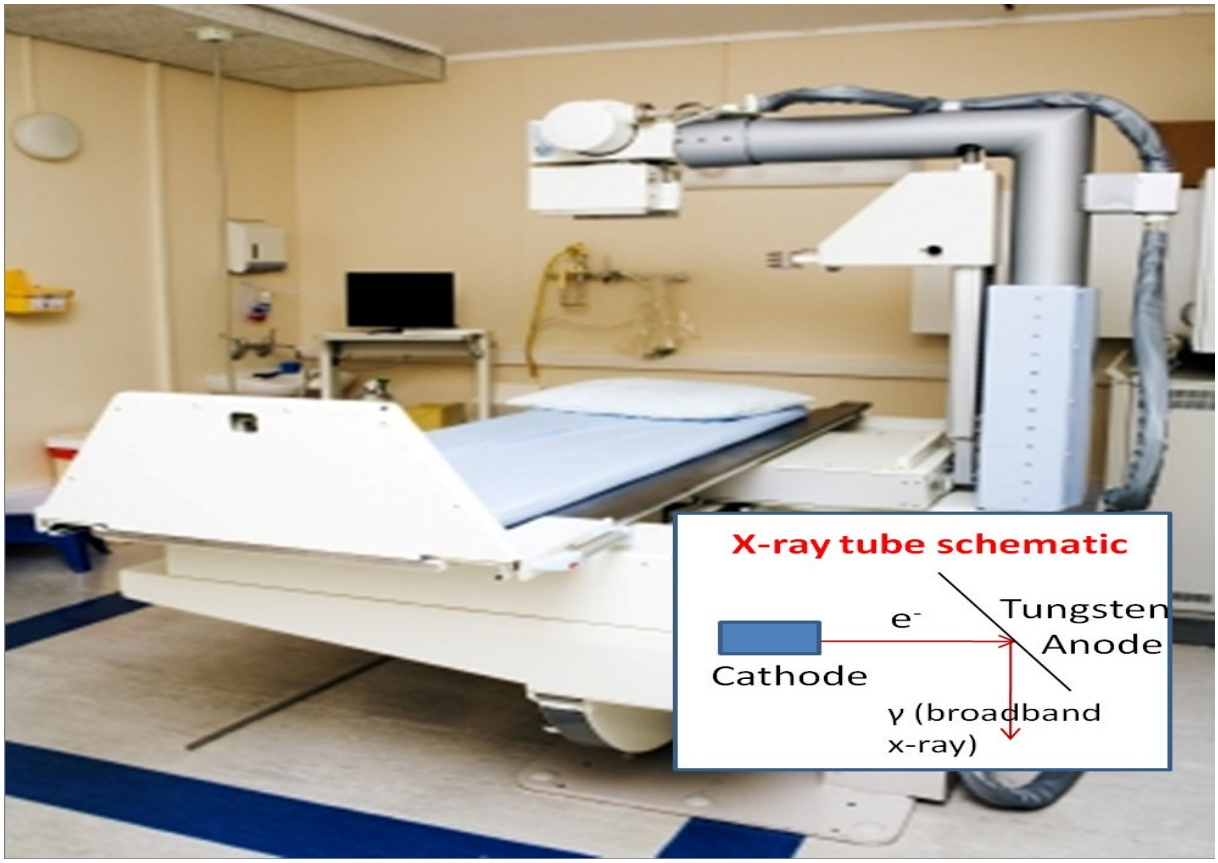
(Pradhan et al 2007, 2009)- Latest Progress:



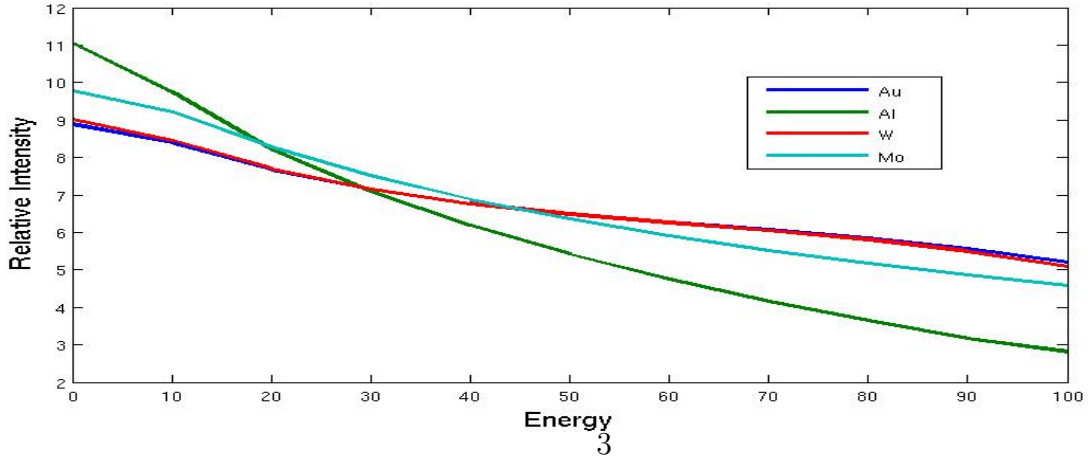
- Left: Full body CAT scans - use high energy broad band X-rays, very high radiation dosages
- Right: RNPT Method - Broadband imaging to Monochromatic Spectroscopy
- Spectroscopy: Accurate info, reduced exposure
- Nanoparticles (NP) are embeded in the tumor and are irradiadated by X-rays for inner shell absorptions leading to ejection of electrons and photons. Electrons breakup the DNA of the surrounding tumor cells - fluorescence to imaging
- Hence the method has several components
- Need: 1) a tunable monochromatic X-ray source
- 2) Heavy element and non- or low toxic NP for absorption of high energy X-rays that are transparent to biogenic elements (H,C,N,O,CHON)
- 3) X-rays at resonant energies of the nanoparticles

X-RAY SOURCES IN MEDICAL FACILITIES

• **Inset: An electron beam accelerates across ΔV between the cathode and the anode, strikes a high-Z target (e.g. W, Z=74), produces bremsstrahlung radiation of energy from zero to the peak voltage as they decelerate;**

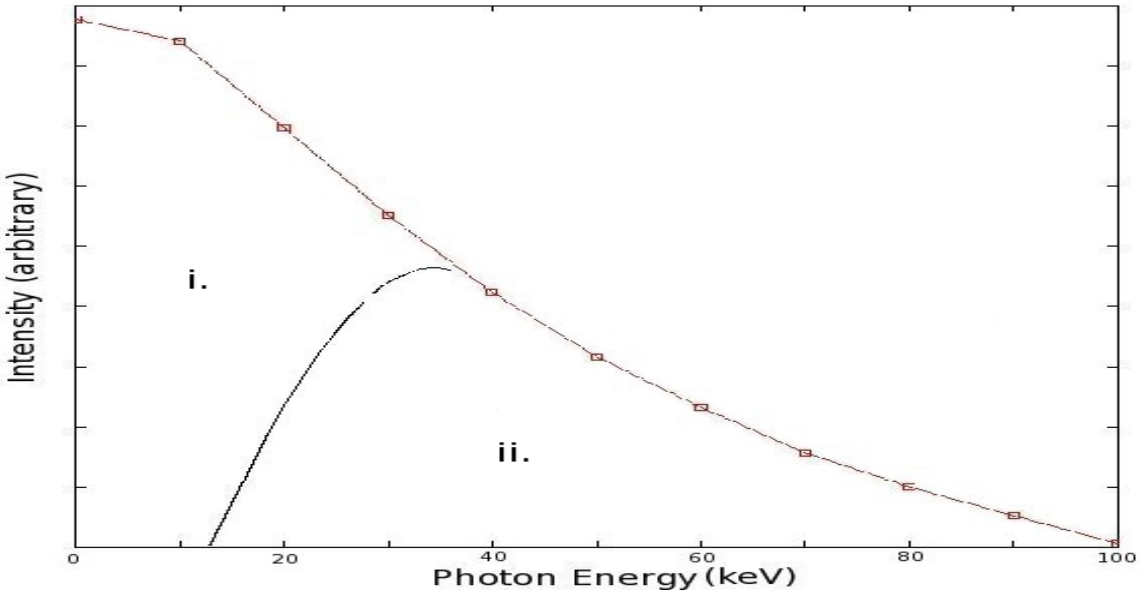


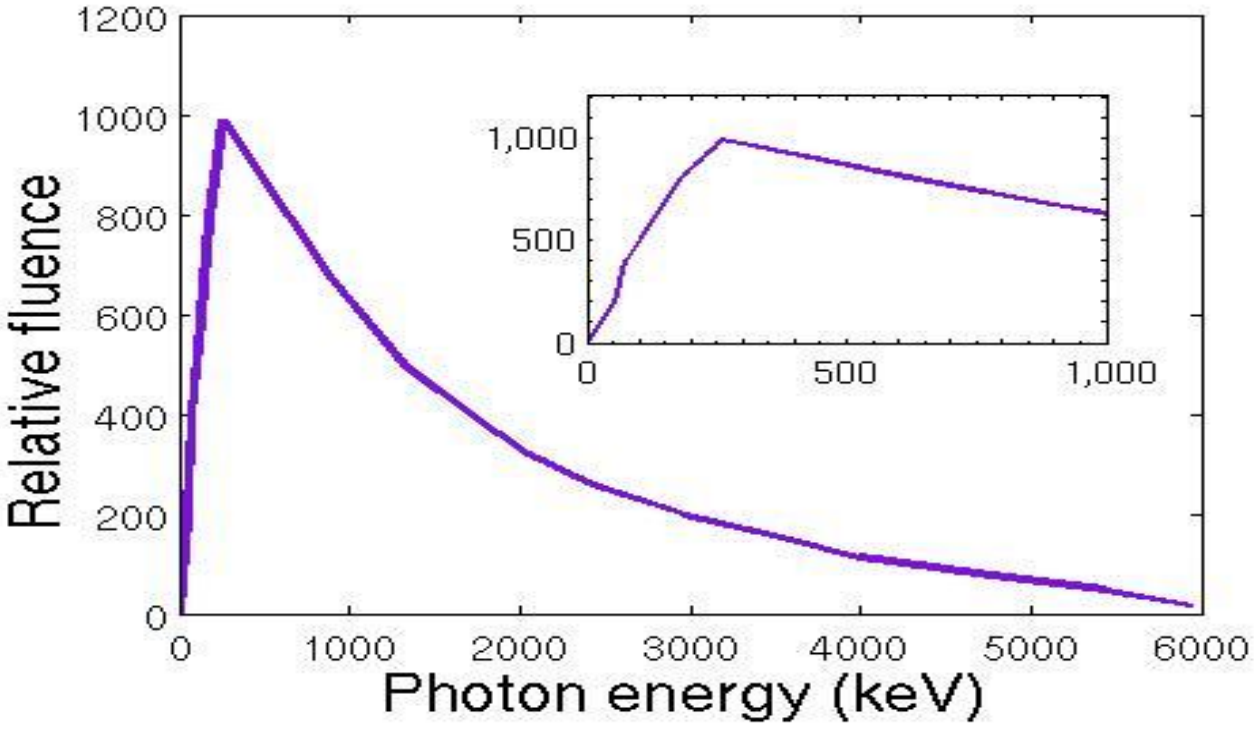
• **Fig: Bremsstrahlung: Al (green), Mo (turquoise) W(red), Au (blue)**



Filtered Bremsstrahlung of an X-ray Machine

- A filter (e.g. Al, dotted) - reduces the harmful low energy radiation
- Bremsstrahlung Max at ~1/3 of kVP or MVp
- Fig: Bremsstrahlung with W target & Al filter





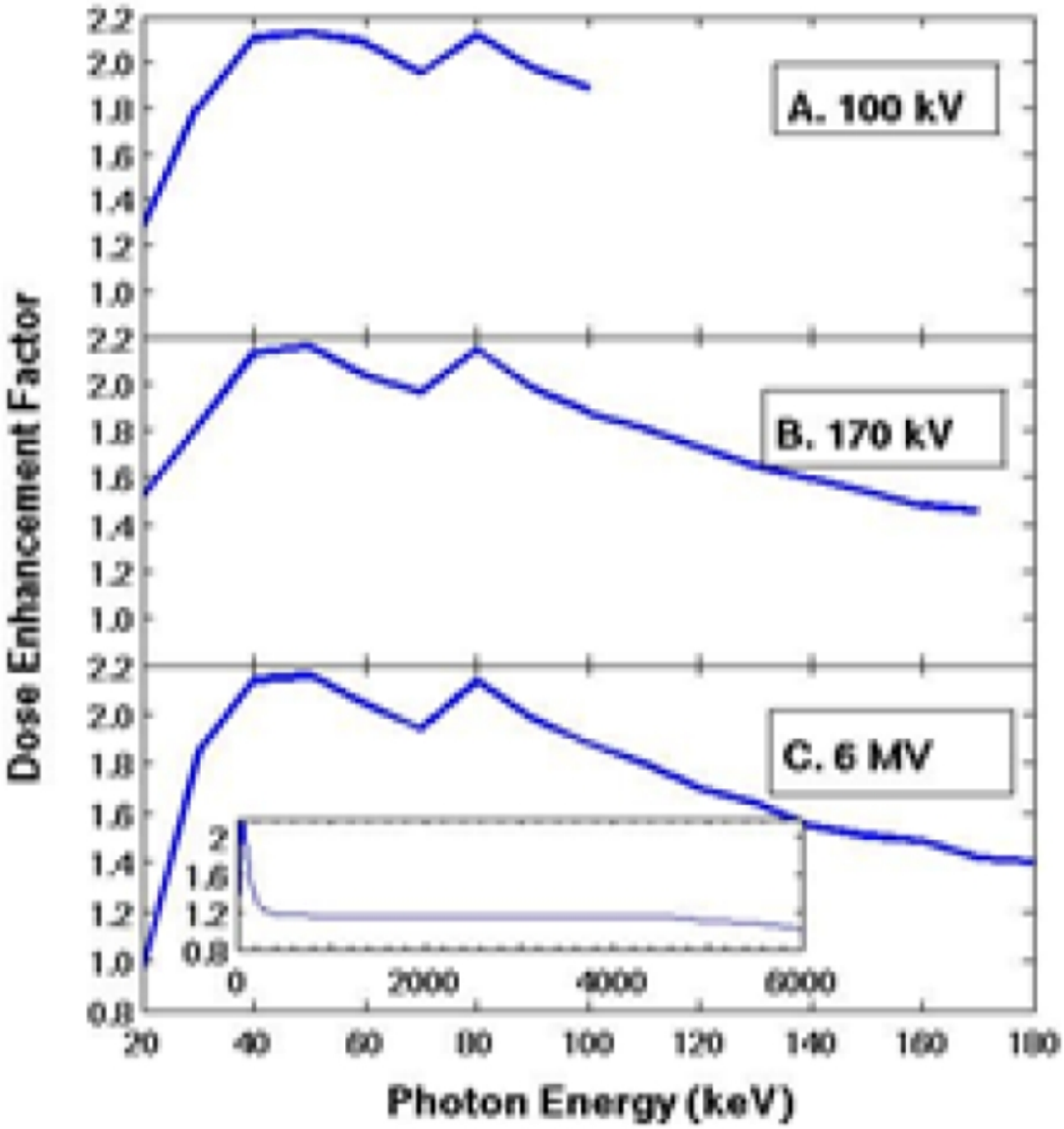
- Bremsstrahlung from a 6 Mev LICAC with a peak around 300 keV from filtering the lower energy x-rays

X-RAY ABSORPTION & DOSE DEPOSITION OF Pt

- **Fig: Monte Carlo Simulation of x-ray dose deposition (Dose Enhancement Factor DEF) in tissues with Pt**

X-ray sources: 100 keV, 170 keV, 6 MeV broadband X-ray sources - 100 keV is efficient (Lim et al 2012)

- **DEF: 1st peak (∼40 keV)- L-shell ionization, 2nd peak (∼ 80 keV - K-shell ionization. Then decays (no more ionization threshold - largely Compton scattering)**



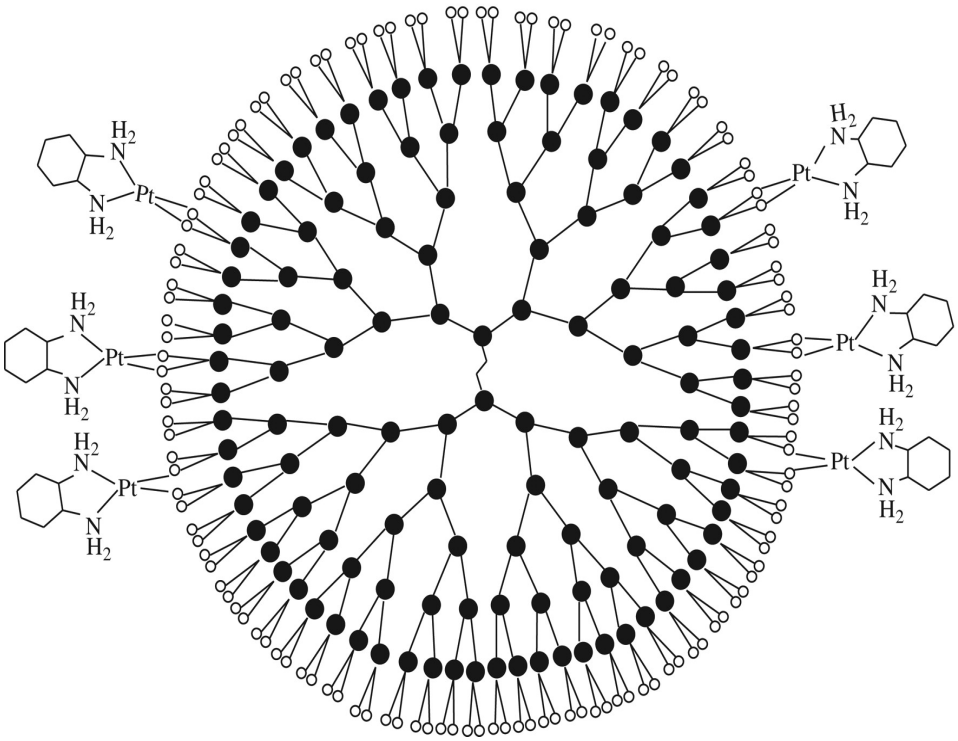
NP: PLATINATED DENDRIMERS

- Dendriver - a delivery vehicle for anticancer drugs; a solution to lowering toxicity of organoplatium drugs
- Can have tunable layers (generations) of structure allowing encapsulation or conjugation of multiple entities either in the core or on the surface
- Have identified an effective conjugate platinated dendrimer - water soluble, low toxicity

Synthesis of PAMAM(G4.5)–[(DACH)Pt] nanoconjugate and a diagram of its structure (other [(DACH)Pt] units omitted for clarity).

$$[(DACH)PtCl_2] \xrightarrow[H_2O]{AgNO_3} [(DACH)Pt(OH_2)_2](NO_3)_2$$

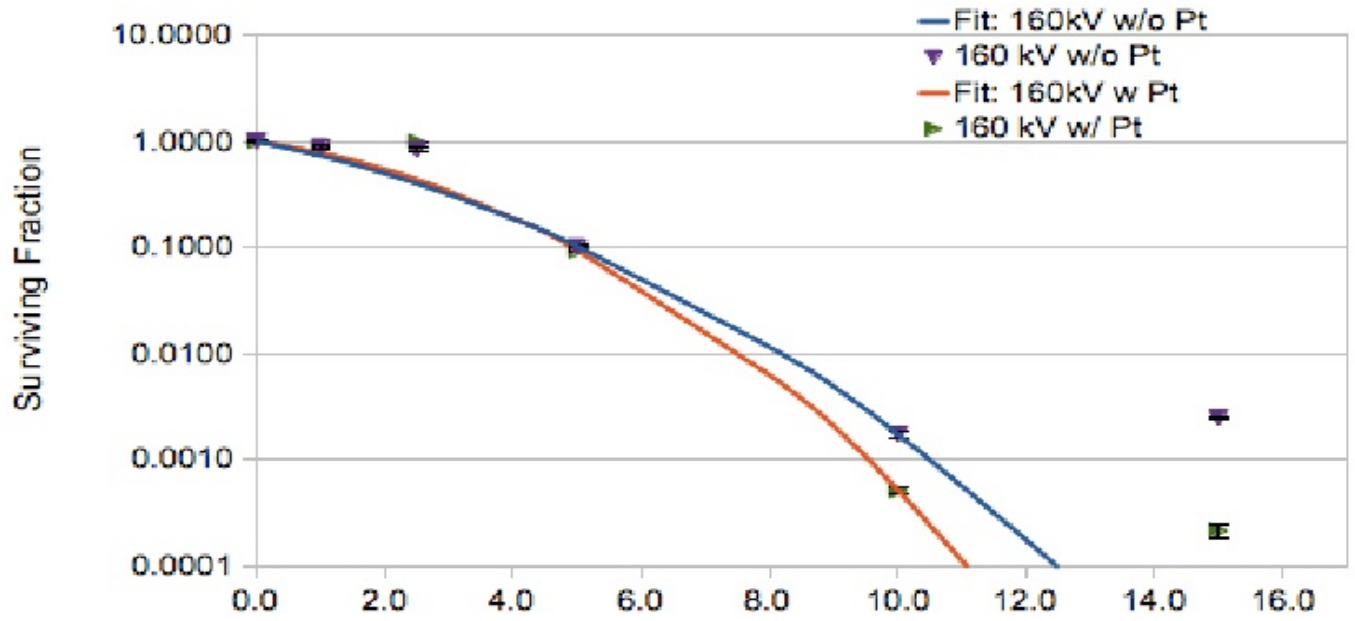
$$[(DACH)Pt(OH_2)_2](NO_3)_2 + PAMAM(G4.5) \longrightarrow PAMAM(G4.5)[(DACH)Pt]$$

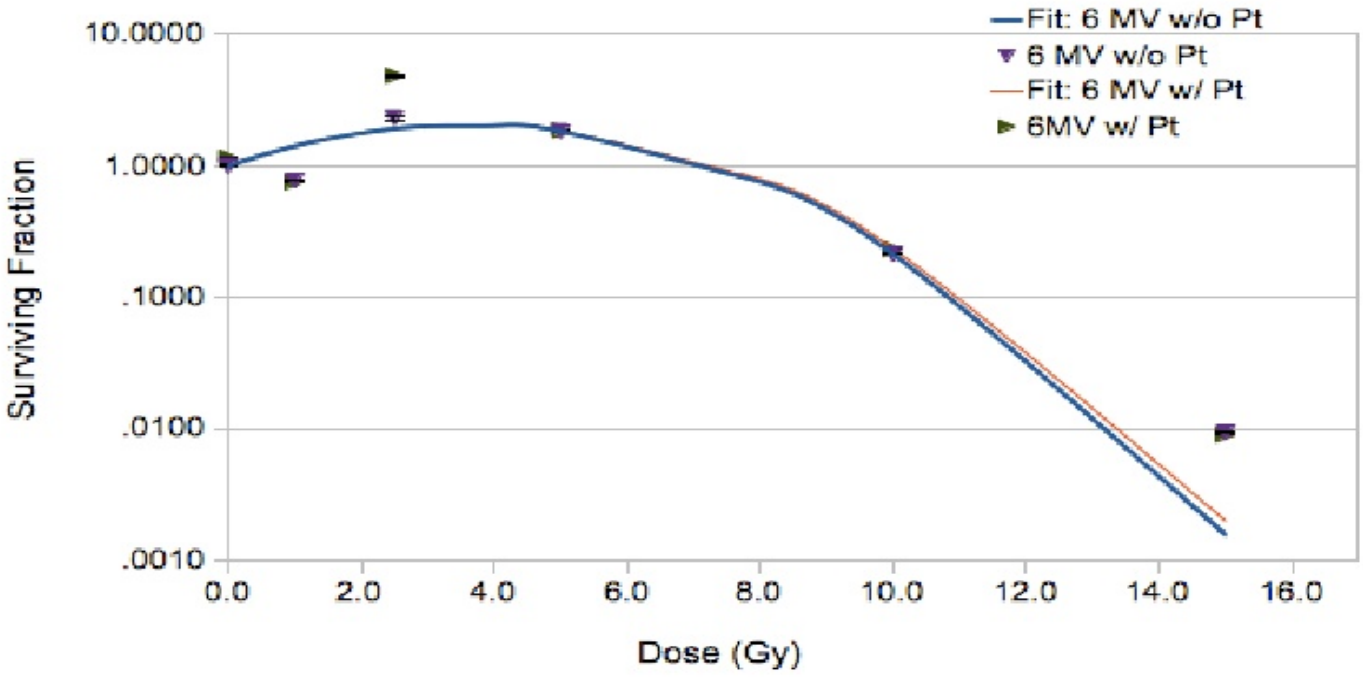


Howell B A , Fan D Proc. R. Soc. A 2010;466:1515-1526

RNPT EXPERIMENT: SURVIVAL OF CANCER CELL (Mouse):

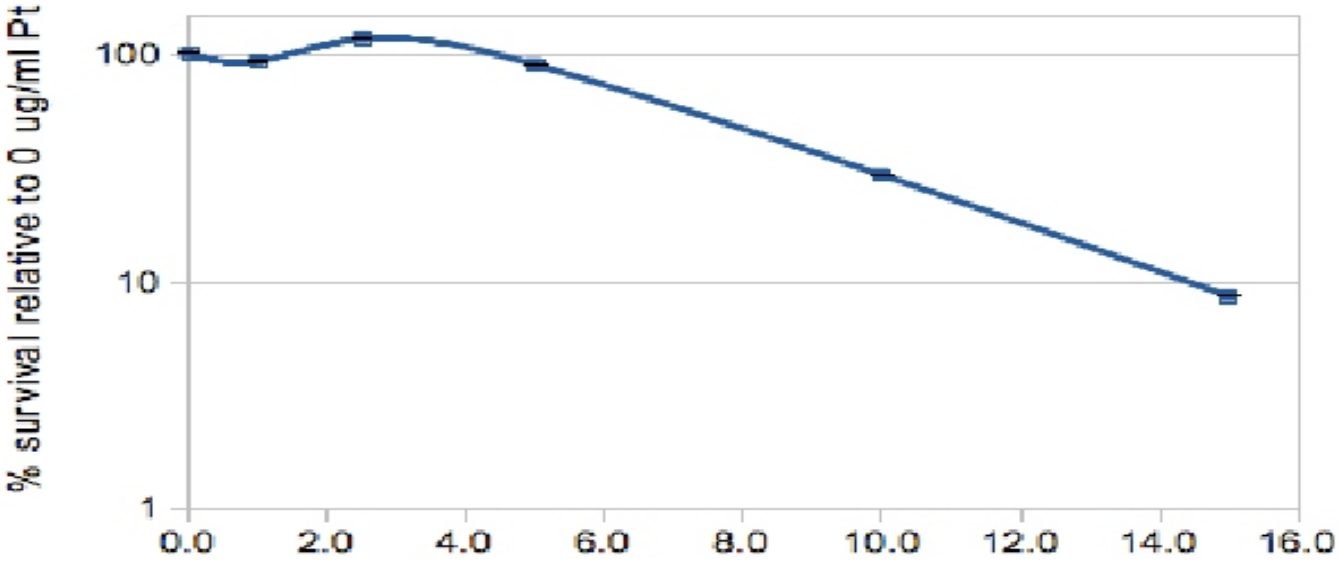
- Study of X-ray energy effect on survival of cultured mouse cancer cells with platinate dendrimers
- X-ray source - Top: 160 keV, Bottom: 6 MeV

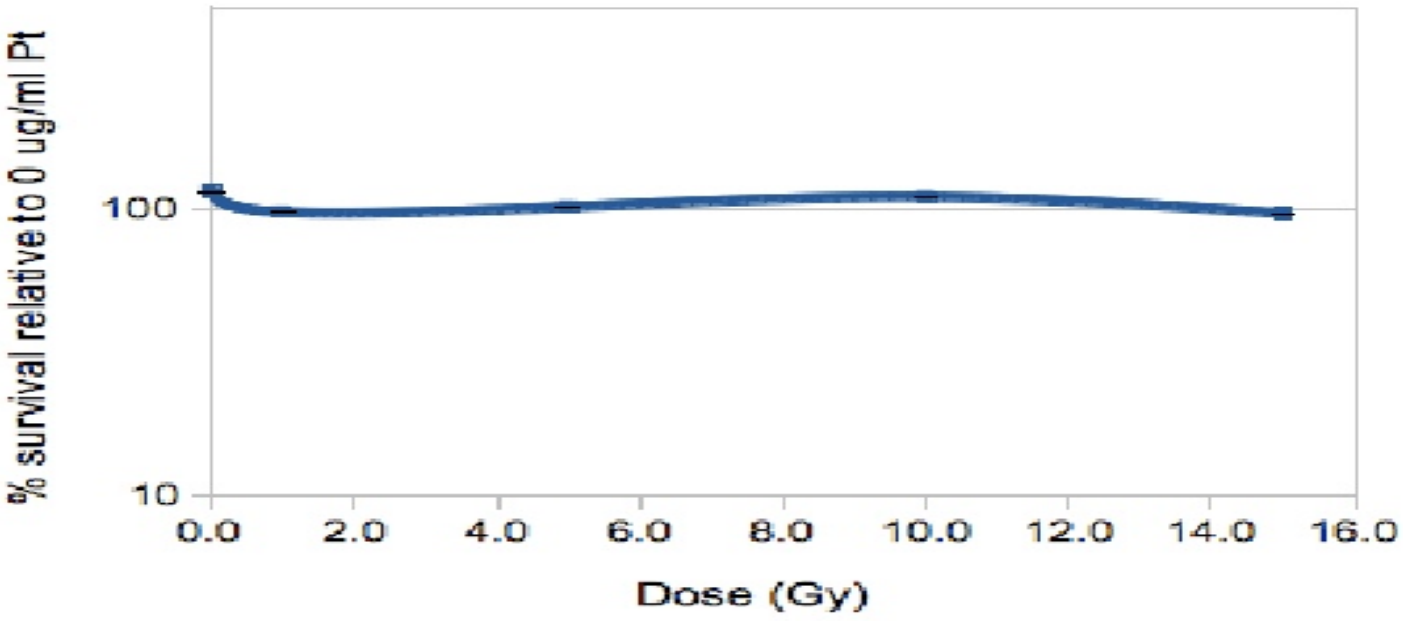




RNPT EXPERIMENT: CANCER CELL SURVIVING FACTOR:

- **160 keV X-rays - suviving factor (SF) goes down with lower energy, 6 MeV X-rays - SF remains constant**
- **Top: 160 keV, Bottom: 6 MeV**





X-RAY INTERACTION WITH NANOPARTICLES *and* Relevant Atomic Parameters

1. Photoexcitation:

$$\mathbf{X^{+Z} + h\nu \rightleftharpoons X^{+Z*}}$$

• **Oscillator Strength (f), Radiative Decay Rate (A-value)**

2. Direct Photoionization (PI) :

$$\mathbf{X^{+Z} + h\nu \rightleftharpoons X^{+Z+1} + e}$$

3. **Photoionization via an Autoionizing State :**

$$\mathbf{e + X^{+Z} \rightleftharpoons (X^{+Z-1})^{**} \rightleftharpoons} \begin{cases} \mathbf{e + X^{+Z}} & \mathbf{AI} \\ X^{+Z-1} + h\nu & \mathbf{DR} \end{cases}$$

The doubly excited state - "autoionizing state" - introduces resonances

• 2 & 3. **Photoionization Cross Sections (σ_{PI})**

THEORY

For a multi-electron system, in nonrelativistic LS coupling:

$$\mathbf{H^{NR}\Psi} = \left[\sum_{\mathbf{i=1}}^{\mathbf{N}} \left\{ -\nabla_{\mathbf{i}}^{\mathbf{2}} - \frac{\mathbf{2Z}}{\mathbf{r_i}} + \sum_{\mathbf{j>i}}^{\mathbf{N}} \frac{\mathbf{2}}{\mathbf{r_{ij}}} \right\} \right] \mathbf{\Psi} = \mathbf{E\Psi}. \tag{1}$$

Relativistic effects: For a multi-electron system, the Breit-Pauli Hamiltonian is:

$$\mathbf{H_{BP}} = \mathbf{H_{NR}} + \mathbf{H_{mass}} + \mathbf{H_{Dar}} + \mathbf{H_{so}} +$$

$$\frac{\mathbf{1}}{\mathbf{2}} \sum_{\mathbf{i\neq j}}^{\mathbf{N}} [\mathbf{g_{ij}(so + so')} + \mathbf{g_{ij}(ss')} + \mathbf{g_{ij}(css')} + \mathbf{g_{ij}(d)} + \mathbf{g_{ij}(oo')}]. \tag{2}$$

where the Breit interaction is

$$\mathbf{H^B} = \frac{\mathbf{1}}{\mathbf{2}} \sum_{\mathbf{i>j}} [\mathbf{g_{ij}(so + so')} + \mathbf{g_{ij}(ss')}] \tag{3}$$

and one-body corrections terms are

$\mathbf{H^{mass}} = -\frac{\alpha^2}{4} \sum_{\mathbf{i}} \mathbf{p_i^4}$, $\mathbf{H^{Dar}} = \frac{\alpha^2}{4} \sum_{\mathbf{i}} \nabla^{\mathbf{2}} \left(\frac{\mathbf{Z}}{\mathbf{r_i}}\right)$, $\mathbf{H^{so}} = \left[\frac{\mathbf{Ze^2\hbar^2}}{\mathbf{2m^2c^2r^3}}\right] \mathbf{L.S}$

ATOMIC PROCESSES:

Transition Matrix elements with dipole operator $\mathbf{D} = \sum_i \mathbf{r}_i$,

$< \Psi_B || \mathbf{D} || \Psi_{B'} >$ → **Radiative Excitation and Deexcitation**

$< \Psi_B || \mathbf{D} || \Psi_F >$ → **Photoionization and Recombination**

$\mathbf{D} = \sum_i \mathbf{r}_i$ → Dipole Operator

The matrix element reduces to generalized line strength,

$$\mathbf{S} = \left| \left\langle \Psi_{\mathbf{f}} | \sum_{\mathbf{j=1}}^{\mathbf{N+1}} \mathbf{r_j} | \Psi_{\mathbf{i}} \right\rangle \right|^{\mathbf{2}} \tag{4}$$

Oscillator Strength. Cross Section, Attenuation Coefficient

• **The oscillator strength (f_{ij}) and radiative decay rate (A_{ji}) for the bound-bound transition are**

$$\mathbf{f_{ij}} = \left[\frac{\mathbf{E_{ji}}}{\mathbf{3g_i}}\right]\mathbf{S}, \quad \mathbf{A_{ji}(sec^{-1})} = \left[\mathbf{0.8032\times 10^{10}}\frac{\mathbf{E_{ji}^3}}{\mathbf{3g_j}}\right]\mathbf{S} \tag{5}$$

Employing the calculated transition rates for the $K\alpha$ resonances, we compute the resonant photoabsorption cross sections

$$\sigma_{\mathbf{K}\alpha}(\nu;\mathbf{K}\rightarrow\mathbf{L_i}) = \frac{\mathbf{4\pi^2 a_o^2\alpha}}{\mathbf{3}}\frac{\mathbf{E(K-L_i)}}{\mathbf{g_k}}\mathbf{S(K-L_i)}\phi(\nu) \tag{6}$$

where the L_i refers to the upper level in the open (ionized) L-shell, $E(K-L_i)$ is the corresponding energy, and $S(K-L_i)$ is the line strength, and the initial level statistical weight $g_K = 1$.

• **We are interested in photoionization of K-shell to initiate Auger process for multiple electron and photon productions**

Auger Cascade: ELECTRON & PHOTON EMISSIONS

• **Fig (i) Photoionization by X-ray photons (E_X) (> K-shell ionization energy E_K) leading to Auger process:**
A higher level electron drops to fill a lower level vacancy, but emits a photon that can knock out another electron.
• **Fig (ii) Multiple electron vacancies due to successive Auger decays lead to cascade of photon and electron emissions**
• **Single ionization of 1s electron can lead to ejection of 20 or more electrons in an ion with occupied O and P shells**
• **Fig (iii) Inverse to Auger - Resonant photo-excitation from 1s → 2p (with L-shell vacancy) by an external monoenergetic X-ray source with intensity above our predicted critical flux (Pradhan et al 2009):**

$$\mathbf{\Phi^c(\nu_{K\alpha}) = \frac{\sum_{n_i \geq 2} g_i A[n_i(S_i L_i J_i) \rightarrow 2(SLJ)]}{g_K B_{K\alpha}}}. \qquad (7)$$

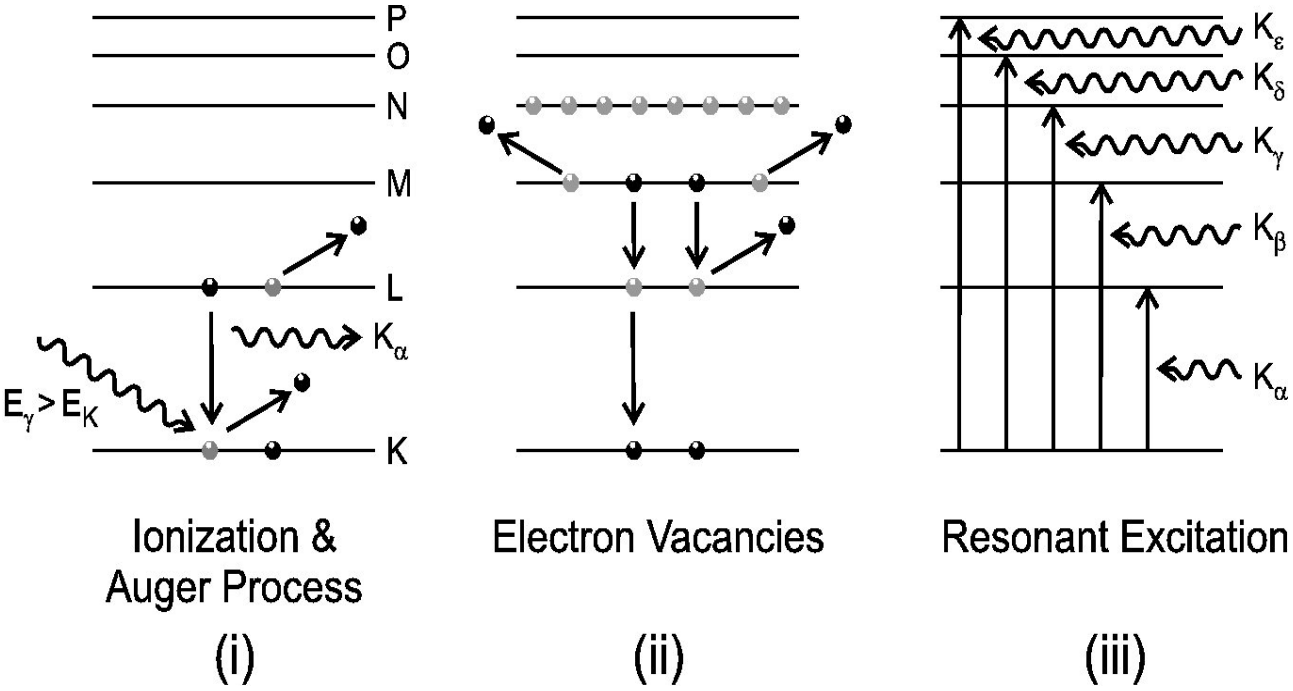


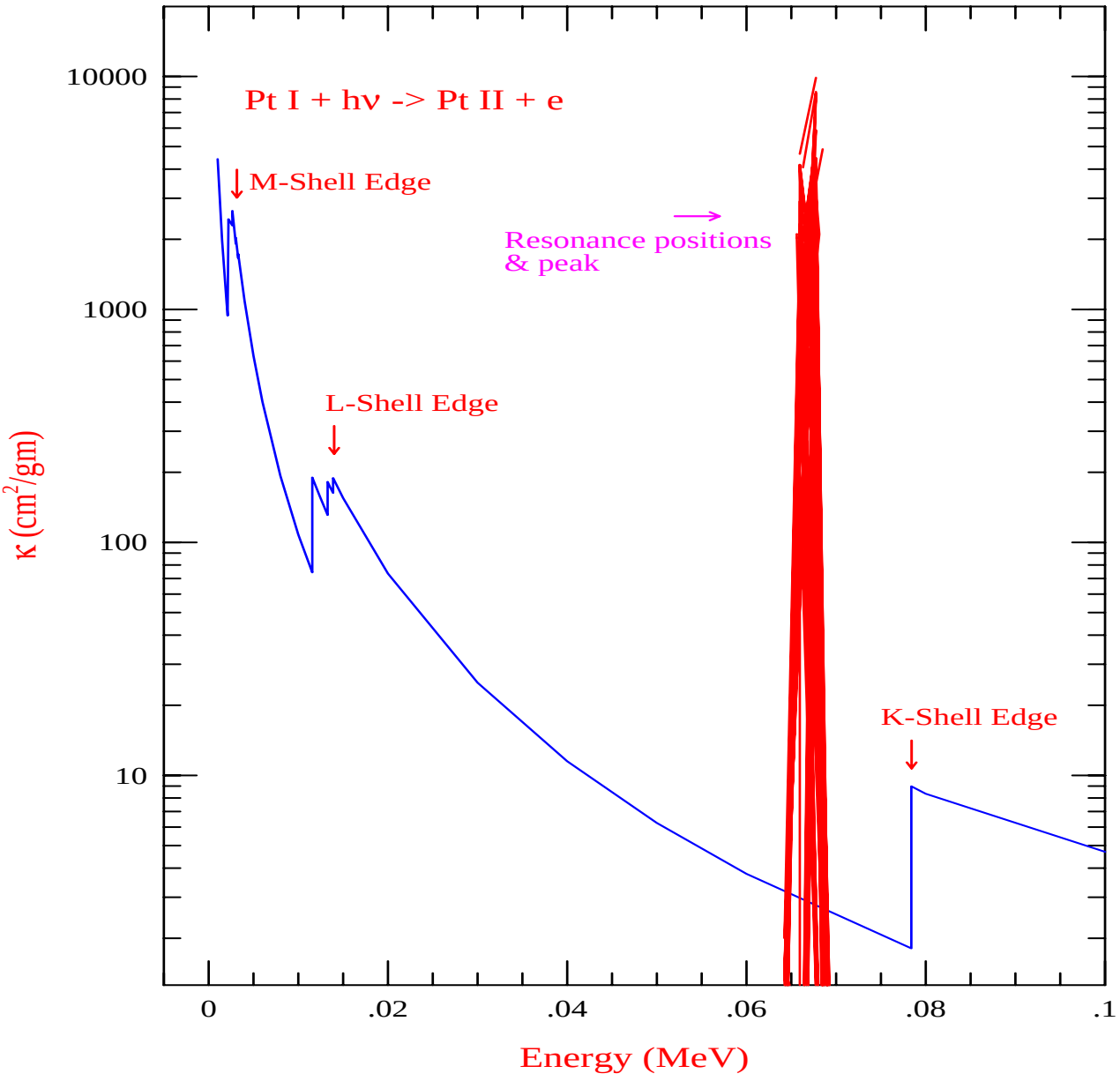
Photo-Absorption Coefficient $\kappa(\mathrm{cm}^2/\mathrm{g})$:

$\mathrm{Pt} + h\nu \rightarrow \mathrm{Pt}^+ + \mathrm{e}$ (Nahar et al 2011)

- Blue curve: Background κ, Red: Resonances below K-edge
- Enhancements in κ $\rightarrow$ at K, L, M (sub)-shells ionization
- Rise at $\mathrm{E_K}$, focus of experiments but without success,
- K-α resonances (red), due to K $\rightarrow$ L excitations, are in $\mathrm{E_{res}}$ = 64 - 70 keV, below $\mathrm{E_K}$

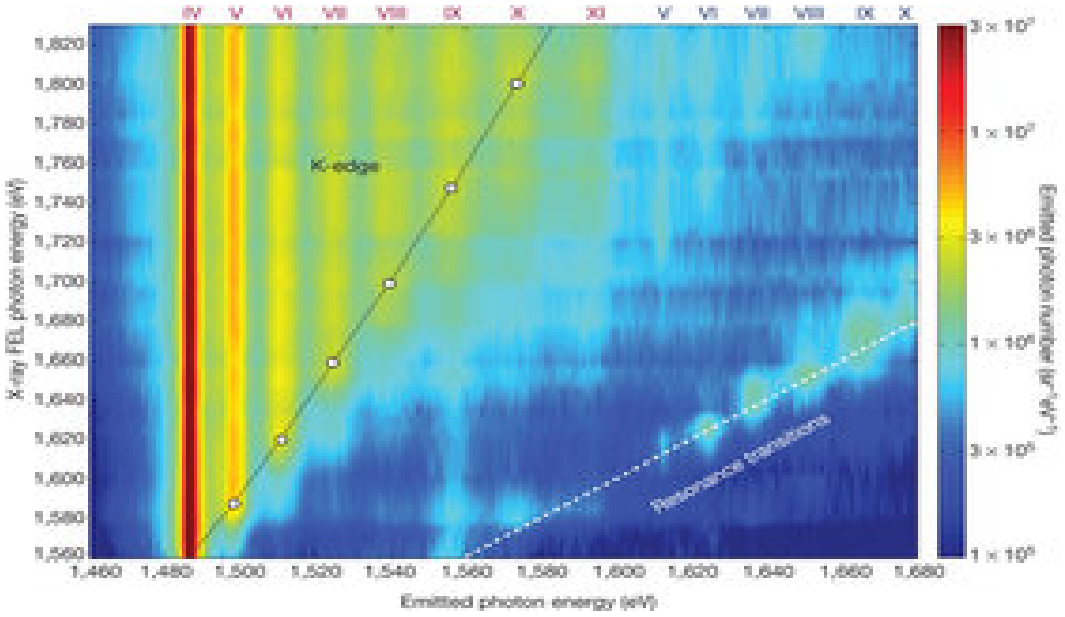
$\rightarrow$ Will increase in ejected electrons in $\mathrm{E_{res}}$

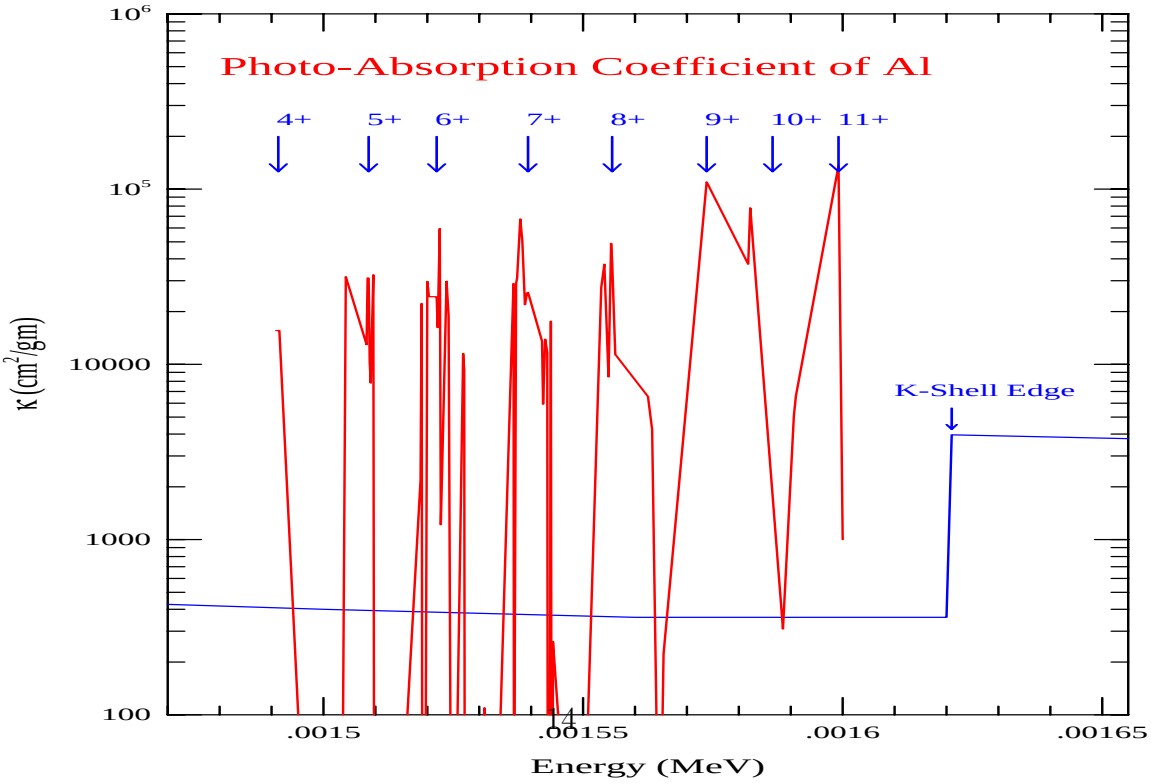
Photo-Absorption Coefficient of Platinum



Resonant K$_\alpha$ Emission Below K-Edge from Various Ionization States of Al

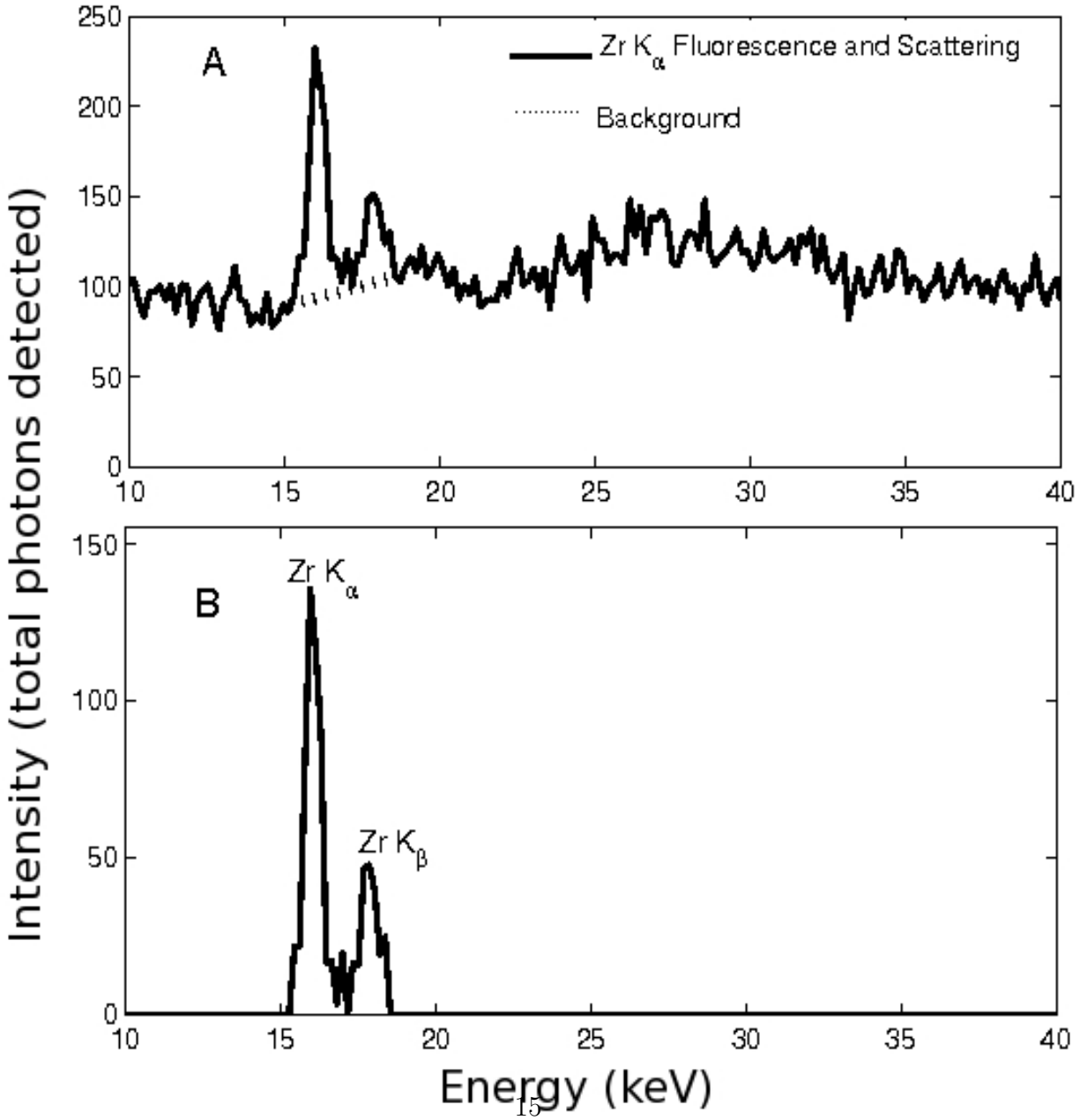
- Top: Berkeley Experiment (Vinko et al, Nature Lett 2012)
- Detected K$_\alpha$ photons at 1.46-1.68 keV below K-edge
- K$_\alpha$ resonances predicted for gold (Pradhan et al. 2009)
- Bottom: Predicted K$_\alpha$ resonances (red) (Blue: background)





Production of Monochromatic X-rays

- **Monochromatic radiation, such as, K_α can be produced by directing the bremsstrahlung, of flux distribution f_B, to a high-Z target (X), rotated at a selective angle**
- **Inner K-shell ionization in the target followed by radiative decays by upper shell electrons can produce X-ray fluorescence at monochromatic energies.**
- **Figure: Production of K_α X-rays from Zr 100 keV bremsstrahlung (Lim et al 2012)**



Flourescence Yield & Intensity of the Monochromatic Beam

• **The K-fluorescence yield ($\omega_{\mathbf{K}}$) can be estimated from the branching ratio:**

$$\omega_{\mathbf{K}} = \frac{\mathbf{A_r(L-K)}}{\mathbf{[A_r(L-K)+A_a(L)]}}$$

A_r**(L - K) = Radiative decay rate for (L** $\rightarrow$ **K),** A_a **= Autoionization decay rate. For high-Z elements, e.g. Pt,** $\omega_{\mathbf{K}} > 0.95$

$\rightarrow$ **All photons from the Bremsstrahlung source above the K-shell ionization energy, E >** $\mathbf{E}_K$**, may be converted into monochromatic** $\mathbf{K}_\alpha$ **radiation with high efficiency**

• **The estimated intensity of the monochromatic energy:**

$$\mathbf{I(K_\alpha) \sim N(X)} \int_{\mathbf{E \geq E_K}}^{\mathbf{E(kVp)}} \mathbf{f_B \sigma_K(E) dE}$$

$N(X)$ **= number density,** σ_K **= K-shell photoionization cross section. For Zr: Efficiency of conversion** $\sim$ **2**

• **The K-fluorescence yield ($\omega_{\mathbf{K}}$) in general produces weaker beam intensity**

• **However, for high-Z elements,** $\omega_{\mathbf{K}} \sim 1$

• **Our effort on producing monochromatic X-rays is continuing**

CONCLUSION

1. **We present progress on our multidisciplinary program on RNPT**
2. **Demonstrated effective energy range for X-rays in the medical X-ray sources**
3. **Presented preliminary results on killing cancer cells using RNPT method**
4. **Demonstrated the resonant energies for Pt and Al for effective Auger process**
5. **Current status on producing monochromatic X-rays**